REMARKS

Claims 16, 17, 19, 20, 22, and 34– 38 are pending in the application. No new claims have been added. No new matter has been added.

The Examiner has indicated in the Advisory Action that the references submitted in the response to final office action filed January 25, 2008 were not considered. Applicants have submitted the references herewith and an IDS to make these references of record. These references demonstrate that administration of adenoviral therapeutics was known by those of skill in the art at the time the instant application was filed. Specifically, the work of Maria Castro et al. has recently demonstrated intracranial adenoviral delivery of Pseudomonas Exotoxin (PE) in an in vivo model. It is noted that Psuedomonas Exotoxin has the same catalytic activity as Diphtheria toxin, the difference being that one toxin has the catalytic subunit at the amino terminus and the other at the carboxy terminus. However, both Pseudomonas Exotoxin and Diptheria toxin cause ADP ribosylation at the diphtherimde residue in EF-2. Castro et al. demonstrate that adenoviral-mediated delivery of Pseudomonas Exotoxin (PE) Fused to IL-13 induces regression of intracranial human glioblastoma xenografts in mice (a copy of the abstract presented at the American Society for Gene Therapy 10th Annual Meeting is enclosed herewith (Seattle, WA. Simultaneous Oral Abstract Sessions: Cancer Gene Therapy (10:15 AM-12:15 PM), Saturday June 2, 2007), previously submitted).

Therefore, contrary to the Examiner's assertion, the methods of the present invention are enabled for methods of delivering the adenovirus as described herein.

In further support of the contention that the claims are not enabled, the Examiner cites the Verma et al., McNeish et al. and Vile et al. references, allegedly disclosing problems with gene therapy. These references describe general concepts regarding gene therapy. In this regard, to date there are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. Thus, while failures may occur, it is important to consider the successes that have occurred in the field of gene therapy.

For example, Applicant wishes to draw the Examiner's attention to the results of gene therapy to treat severe combined immunodeficiency, as disclosed by Blaese et al. (Science 270:475-480 (1995). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. To this day both patients continue to display significant improvement in

their immune system function. The results of this gene therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer context, Roth et al. (Nature Medicine 2(9):985-991 (1996)) have shown that a recombinant retroviral vector targets tumor cells in vivo. Moreover, this vector, which encodes the tumor suppressor p53, provided a sufficient level of p53 expression such that apoptosis, or programmed cell death, was triggered in these cells. Accordingly, retrovirus gene therapy was accomplished in vivo. Khuri et al. (Nature Medicine 6(8):879-885 (2000)) reported a successful gene therapy regimen in human cancer patients using ONYX-015, an oncolytic, chimeric group C adenovirus having a large deletion in the E1B gene.

With respect to X-linked severe combined immunodeficiency (i.e., SCID-X1), Cavazzana-Calvo et al. (Science 288:669-672 (2000)), have demonstrated full correction of disease phenotype in patients treated by gene therapy protocols. Further, Kay et al. (Nature Genetics 24:257-261 (2000)) have demonstrated therapeutic efficacy in the treatment of Haemophilia B with AAV vectors carrying the gene that encodes factor IX.

The successes of gene therapy are not limited to only these examples. According to a 1995 review article (Crystal, Science 270:404, 405 (1995)),

> [p]robably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible . . . [and] most studies have shown that genes can be transferred to humans whether the strategy is ex vivo or in vivo, and that all vector types function as intended.

Clearly, there is evidence to support successful human gene transfer in both ex vivo and in vivo studies.

Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Applicants submit herewith a petition for the appropriate extension of time.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Dated: August 25, 2008

Respectfully submitted,

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